

Career follows the development of allergology

By S. G. O. Johansson, MD, PhD, FAAAAI

In 1960, during the summer vacation, after three years at medical school, I had my first contact with the hospital environment. The medical education did not qualify you to work as a physician and I got an appointment, as an assistant nurse, at the Blood Bank, a section within the Department of Clinical Chemistry at the University Hospital in Uppsala. It was a nice experience and next summer I came back, but now as a lab technician. Working in a laboratory was exciting and when Drs. Johan Killander and Claes Högman asked me to do some specific projects I accepted with pleasure.

Immunology was a hot subject in the early 1960's and it was decided that we should develop a sub-unit with special focus on clinical aspects. Uppsala has a very good tradition in the field of separation and characterization of serum components. Professor T. Svedberg had, at the Institute of Biochemistry, University of Uppsala, invented the ultracentrifuge concept and Professor Arne Tiselius the electrophoresis, and both of them were awarded a Nobel Prize. To take advantage of this knowledge, I was asked to establish immuno-electrophoresis for characterization of immunoglobulins and also, as part of our ambition to develop clinical immunology, to study sera from patients with suspected immunological diseases. In Tiselius' laboratory Hans Bennich was working as a research student. A collaboration was started and soon formalized as a research group with Högman, Killander, Bennich and me with the aim to isolate and characterize human immunoglobulins.

With time Bennich and I integrated our studies more and more. Bennich was interested in isolation and characterization of human immunoglobulins which included fragmentation with reduction/alkylation and digestion by proteolytic enzymes. I raised antisera in rabbits to identify the various fragments but also to set up immuno assays to characterize and quantitate the three known immunoglobulin classes and their constituents, to support clinical investigations of patients with suspected disturbances in this area, e.g. immune deficiencies and multiple myeloma. The latter group was of special interest since plasma from such patients was useful for Bennich's preparative work. A patient with an IgA myeloma for instance, could have a serum IgA concentration 100 times higher than a normal individual and, as a bonus the other immunoglobulins had reduced concentrations.

In June of 1965 I found a myeloma protein that did have light chains, as do all immunoglobulins, but I could not identify the isotype. It was indeed an immunoglobulin with lambda light chains, unique antigens on the Fc fragment and a molecular weight in the order of 200 000 Daltons, indicating it represented a new immunoglobulin isotype, which we provisionally called IgX. A detailed description of the development from IgX to what in 1968 was designated IgE, was recently published in *J. Allergy Clin. Immun.* (2005; 115:644-648). At the department of Clinical Chemistry Dr. Leif Wide was working on immuno assays for hormones. His hemagglutination technique for HCG was developed for IgX. In January 1967 IgX was detected in serum of healthy persons and thus fulfilled all criteria for a new immunoglobulin isotype which we, according to praxis at that time, provisionally designated by the initials of the individual from which it was derived, IgND. As a result, some clinical applications in the pipeline, e.g. the finding of increased levels of IgND in allergic asthma and the development with Wide of the test for IgND antibodies to common allergens, RAST, were finalized and published. Interestingly, these two approaches to describe serological events in allergy are still the basis of in-vitro diagnosis of IgE-mediated allergy.

During 1966 much effort was invested in understanding IgX. During this period Bennich had a visiting scientist, Dr. Mac Turner, from Birmingham. He had experience of working on immunoglobulins with Dr. D. R. Stanworth and Dr. D. S. Rowe. Stanworth had spent a lot of time characterizing reaginic activity to horse dander allergen by the Prausnitz-Küstner test, and Rowe, on a sabbatical at Johns Hopkins, had just discovered IgD. Close contacts with experts, national and international, is of great value in research. Thus, a collaboration was started with Stanworth aimed at testing if IgX could block the P-K reaction, which was the case, and later to characterize the structure responsible for this activity, which was found to be the Fc-fragment of IgND.

From the fall of 1966 we had close contacts with Rowe, then at the WHO International Reference Centre for Immunoglobulins in Lausanne. We sent them purified IgND immunoglobulin, fragments of IgND and antisera specific for the two antigenic epitopes we had found on the Fc fragment and they could confirm our findings.

In 1966-1967 **Kimishige Ishizaka, MD, FAAAAI** and **Teruko Ishizaka, MD, FAAAAI**, then in Denver, had published their findings on γE , reporting that their anti- γE could block the P-K reaction with ragweed allergen and that, when injected in the skin, it gave an erythema, hence the "E." About February/March, 1967, we sent a mail informing them of our finding of IgND, and invited them to a comparison with their γE . When it was found, and confirmed, that their anti- γE reacted with isolated IgND and that anti-IgND inhibited the reaginic activity of their γE -containing fractions, the contacts with WHO intensified. In February, 1968, a workshop was held at the Reference Centre in Lausanne with Kimishige Ishizaka representing the γE leg and Bennich and I the IgND leg of what was then, for the first time, officially accepted as a new class of human immunoglobulins, designated IgE (Bull World Health Organ 1968; 38:151-152).

During the following years I became pretty busy. In May of 1968 Bennich and I passed our dissertations at the University of Uppsala, Faculty of Medicine and became Doctors of Medicine. The University kindly provided us both with a three year research position as assistant professors which, for the first time, allowed us to fully concentrate on research. Since our initial findings on IgND were published in the Lancet, the message spread quickly. In 1968 I participated in my first congress of the European Academy of Allergology and Clinical Immunology, EAACI, held in Florence, Italy, and heard Professor Jack Pepys, MD teach us how to pronounce "budgerigar." In 1969 we presented our data at the Royal Society of Medicine in London invited by Dr. J. L. Turk and the same year we visited for the first, of many times, Drs. Ishizaka, in Denver. A few years later **Sheldon C. Siegel, MD, FAAAAI** invited me to my first Annual Meeting of the American Academy of Allergy and Immunology, nowadays AAAAI, held in San Francisco in 1972, to present our findings. At the meeting AAAAI kindly nominated me International Fellow, the first appreciation I had the pleasure of receiving from an allergy society! International congresses are such an important part of research; you get a chance to hear latest news, but more importantly, to develop personal relationship with scientists in the field. For me they were also good experience for the large, international ones I organized in Stockholm 1994 and 1998.

In the meantime **I. Leonard Bernstein, MD, FAAAAI** at the University of Cincinnati had invited me to spend some time with him and his group as Visiting Professor, and during 1972-1973 I had the pleasure of staying in Cincinnati with my family; an interesting scientific experience for me and a social challenge for my wife Anna-Stina and the children. To work as Postgraduate in an active laboratory is an important experience that should be part of all scientists' careers. During the 1970's I was invited several times to the United States and enjoyed visiting with many of the very best scientists and research centres in the field of allergy and immunology. Just a few examples: **K. Frank Austen, MD, FAAAAI**, and **Albert L. Sheffer, MD, FAAAAI** in Boston; **Phillip S. Norman, MD, FAAAAI**, and **Lawrence M. Lichtenstein, MD, PhD, FAAAAI**, in Baltimore; **John A. Anderson, MD, FAAAAI** in Detroit; **Roy Patterson, MD, FAAAAI**, in Chicago; and **Gerald J. Gleich, MD, FAAAAI** at the Mayo Clinic. Interestingly, all except one of those notable individuals became President of AAAAI.

As assistant professor in Uppsala working at the University Hospital, I had good opportunities to study IgE in allergic diseases. Many doctors joined my group and prepared a thesis in medicine as part of their specialization. Most aspects of allergology were studied, e.g. Drs. Torsten Berg and Tony Foucard in Pediatrics, Dr. Hans Deuschl in ENT, Olle Zetterström, MD in lung medicine and Dr. Sven Öhman in dermatology. These close collaborations led to life-long friendships and to increased understanding of each other's field of expertise. We used to say that we expected that "You pick up 20% of my knowledge, and I will do the same with yours." I think it is very useful that the laboratory scientist has some understanding of the patient's situation and the clinician should know what it is realistic to expect from the laboratory.

In the late 1970's I was approached by Dr. B. Samuelson, then Rector of the Karolinska Institute, and invited to apply for a position as Professor of Clinical Immunology, at the Karolinska Institute, combined with being head of the Department of Clinical Immunology, later also including Transfusion Medicine, at the Karolinska Hospital. I accepted, of course, and started my work in the summer of 1980. Since this was a new discipline at Karolinska I had to build up the organization from scratch. It is not so easy to handle people, equipment, money and politicians when your experience is based on immunizing rabbits and performing immunochemical laboratory bench work. However, thanks to dedicated co-workers the department has developed nicely. We were three persons, I had a secretary and a lab technician, from the start and today we are about 50 in Clinical Immunology, with two additional professors, Annika E. Scheynius, MD, PhD, and **Marianne van Hage, MD, PhD, FAAAAI**. Active, internationally recognized, research is going on in our department in several areas of allergy, e.g. recombinant allergens for diagnosis and treatment in collaboration with Dietrich Kraft, MD and Rudolf Valenta, MD, in Vienna and Reto Cramer in Davos, Austria, the role of staphylococcal enterotoxins with Claus Bachert, MD, PhD, in Ghent, Belgium, identification of persons at risk

for anaphylaxis during anaesthesia in collaboration with Dr. Erik Florvaag in Bergen, Norway, and mechanisms of inflammation where Joachim B. Lundahl, MD, is heading a group collaborating with, amongst others, **Judah Aryeh Denburg, MD, FRCPC, FAAAAI**, in Hamilton, Canada.

In addition to building up a Department of Clinical Immunology I was also involved in administration within the Karolinska Hospital. During 1984-1989, as one of the Chief Physicians, I was responsible for the hospital's obligations to all clinical research. That was an interesting time that gave me a lot of experience, as were the six years in the scientific committee of the HRH Queen Silvia of Sweden Foundation for Research on Children's Handicap. During two periods I had the pleasure of working as President of the Swedish Association of Allergology (SFFA) and when I was elected a member of the Executive Committee of EAACI and 1992 became President of EAACI this experience was very useful. During my term we fulfilled some of the intentions of my predecessors, like **A. Barry Kay, MD, PhD, FAAAAI**, London and **Francois-Bernard Michel, MD, FAAAAI**, Montpellier. We updated the infrastructure of EAACI, engaged a professional executive office, introduced individual membership, made a deal with the publishers of Allergy to make it the official journal of EAACI, and negotiated a long term sponsor agreement with a group of companies, the so called "Founder Sponsors." The finances were in the good hands of Dr. Brunello Wüthrich, Zürich. When my 10 years as Editor-in-Chief of Allergy expired in 2002, it was a pleasure to hand over the responsibility to **Jean Bousquet, MD, FAAAAI**, of Montpellier, who is doing a great job. EAACI has developed nicely, chaired most recently by presidents Dr. Paul Van Cauwenberge, Ghent and Ulrich Wahn, MD, Berlin.

Immediately after my term in EAACI in 1997 I had the pleasure of being nominated President of IAACI. Again it was time for an updating. The first major step was to change the name to World Allergy Organization (WAO) and to take a responsibility for global communication within the world of allergy. Working in close collaboration with Karen Henley Davies of London, I have had the pleasure of introducing new ideas such as the educational program GLORIA and with Richard F. Lockey, MD, FAAAAI, the Web site. At "my congress," actually it was **Constance H. Katelaris, MD, PhD, FAAAAI's**, show, in Sydney year 2000 I became "past." However, as with EAACI, I think it is fair to say that WAO is doing fine and living up to our expectations, thanks to preceding presidents like Terumasa Miyamoto, MD, of Tokyo and Alberto Oehling, MD, of Pamplona and I am delighted at the way the organization has continued to grow under the direction of my Presidential successors, **Allen P. Kaplan, MD, FAAAAI**, of Charleston and Carlos E. Baena-Cagnani, MD, of Cordoba. We have great trust in the upcoming president, **Michael A. Kaliner, MD, FAAAAI**, Washington and the new Editor-in-Chief of the WAO Journal.

Over the years I have had the honor and pleasure of receiving many international and national awards. However, in 1992 the Swedish Allergy Society kindly nominated me to become an Honorary Member. This was most rewarding for two reasons. To be recognized by an allergy society means that the allergy specialists, the people actually working in the field of allergy and having seen the situation for their patients change, do appreciate our work. And secondly the Swedish society was my first, although we all know "it is not easy to be a prophet in your own country." Today 20 or so national societies have kindly nominated me be a Honorary Member, including AAAAI, ACAAI, Argentinian Allergy and Immunology Association, British Society for Allergy and Clinical Immunology, German Society for Allergy and Clinical Immunology, Korean Society of Allergology and Swiss Society of Allergology and Immunology, to mention just a few of them.

I have had the opportunity to follow the development of allergology from something that was not always fully understood and appreciated to a highly respected, scientifically documented medical specialty. Recently I have been engaged in promoting the revised nomenclature of allergy, endorsed by EAACI and WAO and its 70 membership societies. Hopefully, now when we better understand each other, our field of expertise can continue to flower and develop.